Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

8597 '00 DEC -4 A10:48

RE: Docket No. 99F-2673

November 26, 2000

Dear FDA:

We strongly object to your approval of irradiation on alfalfa and other sprouting seeds for the control of microbial pathogens. Although there have been a few cases of sprout contamination by E. coli 0157H7, we feel that the E. coli problem should be solved on the farm where it originates, not by subjecting numerous off-farm foods that have been contaminated by farm manure and farm water run-off, to ionizing radiation. The problem (including contamination of well water) needs to be corrected at its farm source.

Consumers United for Food Safety (CUFFS) has followed the food irradiation issue since 1982 and has questioned the deficient, flawed and contradictory studies used to justify the approval of irradiation for numerous foods. Public Citizen has written a referenced criticism of the FDA's handling of food irradiation petitions (A Broken Record, October 2000, available at www.citizen.org/cmep). We concur with their summary that the proper and necessary toxicological studies have not yet been done to guarantee the safety of the mass consumption of irradiated foods. We also feel that the present FDA is losing its credibility and has become "politicized" by Congressional budget riders.

In the FDA approval of irradiation for sprouting seeds, no toxicity studies were done on the sprouts from irradiated seeds. Moreover, we think it is scandalous not to label sprouts from irradiated seeds. We urge you to reevaluate your approval and most certainly to correct the lack of consumer labeling.

Sincerely,

Connie Wheeler

Connie Wheeler, Managing Director
Consumers United for Food Safety
P.O. Box 22928
Seattle, WA 98122
425-747-2659

99F-2673

C 10

CONSUMERS UNITED
FOR FOOD SAFETY

P.O. Box 22928 Seattle, WA 98122

HFA
305

3 SEATTLE WA 981
PM
27 NOV
2000

33 USA
HAPPY
"WHO-LIDA
U.S. Postal Ser

Dockets Management Branch
RE: Docket No. 99F-2673
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

The following text was extracted from the FDA Talk Paper on this topic:

> "... prescribers should be aware that patients with severe influenza-like illness, especially those who have chronic medical conditions, may have significant bacterial infections (either instead of influenza, or in combination with influenza). Anti-viral products such as those approved for flu have no activity against bacterial infections and patients should be treated with appropriate antibacterial therapy whenever bacterial infection is suspected. FDA has received reports of patients with serious bacterial infections who initially had influenza-like symptoms and who had progression of bacterial infection during treatment with antiviral drugs alone." [4]

Volume of Antibiotic Use Data

In linking surveillance data to volume of antibiotics used, it is important that other information such as dose and duration is known in order to provide a better prediction of the drivers for resistance. Determining volume dispensed without an understanding of actual use is of very limited utility.

Surveillance Systems

SmithKline Beecham endorses the development and implementation of a coordinated monitoring plan for antimicrobial resistance at the local level using standardized tests and has responded affirmatively to such a proposal in the CDC Draft Action plan. [5] SmithKline Beecham strongly endorses the use of these universally accepted standard tests and believes that this is critical to the consistent and meaningful interpretation of the surveillance data throughout the US. These standards need to be in place prior to collection and collation of surveillance data. Without universal standards, collated surveillance data would be difficult to interpret, and the surveillance would be of very limited value.

SmithKline Beecham believes that pharmacokinetic and pharmacodynamic data are important to provide clinically relevant information about the ability of an antibacterial agent to eradicate an infecting pathogen, and hence minimize the potential to develop resistance. These data can provide information to help ensure that the correct drug is administered to eradicate the pathogen and cure the infection the first time. We believe that there should be greater emphasis on the use of the pharmacokinetic and pharmacodynamic (PK/PD) relationship to provide clinically relevant data that establish which antibiotics are likely to maximize efficacy, and minimize the risk of the development of bacterial resistance. This is in line with the FDA Anti-Infectives Advisory Committee's recommendation that the PK/PD relationship for an antibacterial medicinal product should be investigated during the drug development program. The Committee reviewed evidence to suggest that in a number of settings, properly conducted studies looking at PK/PD can provide measures that will correlate with clinical outcomes. [6]

Scope of the Proposal

SmithKline Beecham questions FDA's reasons for excluding drugs to treat tuberculosis from this proposal. Patient information regarding the continued ingestion of such medication is imperative to prevent resistance from developing both for the patient and the population at-large.

Summary of General Recommendations for Labeling Statements

SmithKline Beecham recommends that the proposed labeling changes be amended as follows:

- A clear and concise definition of appropriate use of antibiotics should be provided that mentions the use of the most appropriate antibiotic at the correct dose and duration for the condition and the known or suspected microorganism being treated.

- Inclusion in the Clinical Pharmacology section of the labeling of a summary of the pre-clinical and clinical data regarding pharmacokinetic and pharmacodynamic parameters to predict clinical response and minimize development of resistance. If such data are lacking, this should be mentioned.

- A local monitoring plan for antimicrobial resistance, with 'standardized' testing, should be developed.

- Physicians should be cautioned to prescribe antibiotics only for known or suspected bacterial infections. Patients should be encouraged to take the medication exactly as prescribed and to take all prescribed doses even if they feel better or are 'totally well'.

Specific Comments Regarding Proposed Labeling Text

FDA Proposed Text

Sec. 201.24 Labeling for systemic antibacterial drug products: required statements.

The labeling of all systemic drug products indicated to treat a bacterial infection, except a mycobacterial infection, must bear the following statements:
(a) At the beginning of the label, under the product name, the labeling must state:
Inappropriate use of (insert name of antibacterial drug product) may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of (insert name of antibacterial drug product) and related antimicrobial agents.
Use (insert name of antibacterial drug product) only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. See Indications and Usage section.

SB Response: Recommend deleting all of these statements under (a), as they are redundant and repeated verbatim under 'Precautions'.

FDA Proposed Text

(b) In the Clinical Pharmacology section, the labeling must state:
Appropriate use of (insert name of antibacterial drug product) includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile.

SB Response: In this section, the labeling also should include a summary of the pre-clinical and clinical data regarding pharmacokinetic and pharmacodynamic parameters to predict clinical response and minimize development of resistance. If such data are lacking, this should be mentioned.

FDA Proposed Text

(c) In the Indications and Usage section, the labeling must state:
Local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of (insert name of antibacterial drug product) for the treatment of the indications listed below. Because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens.

SB Response: No changes are suggested

FDA Proposed Text

(d) In the "Precautions" section, under the "General" subsection, the labeling must state:
Inappropriate use of (insert name of antibacterial drug product) may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of (insert name of antibacterial drug product) and related antimicrobial agents.
Use (insert name of antibacterial drug product) only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. See Indications and Usage section.

SB Response: A definition of appropriate use should be provided such as, "Appropriate antibiotic use requires the selection of an antibiotic, for a known or suspected bacterial infection, that optimizes clinical therapeutic effect by maximizing bacteriological eradication and minimizing the development of resistance and drug-related toxicity. In order to eradicate the bacteria and minimize the development of bacterial resistance, it is important to administer the appropriate antibiotic at the right dose and for the right duration. See Dosage and Administration section."

FDA Proposed Text

(e) In the "Precautions" section, under the "Information for patients" subsection, the labeling must state:
Patients should be counseled that (insert name of antibacterial drug product) should only be used to treat bacterial infections. It does not treat viral infections (e.g., the common cold). Patients should also be told that the medication should be taken exactly as directed. Skipping doses and not completing the full course of therapy **(despite feeling better or 'totally' well)** may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop that will not be treatable by (insert name of antibacterial drug product) **or other antibacterials** in the future.

SB Response: Suggested additions are bolded.

In summary, SmithKline Beecham strongly supports efforts to curb the development of antimicrobial resistance. Actions such as widespread incorporation of precautions in labeling should be based on sound evidence that the desired results occur without a compromise in patient outcomes. Continuing efforts must be made to better understand the drivers of antimicrobial resistance to guide future actions. 'Appropriate' use of antibiotics should not be simplistically equated to a reduction in volume of use. Antibiotics should be used only when a bacterial infection is known or suspected. Selection of an antibiotic and dosing regimen should be based on reliable data that will provide the best opportunity for a favorable clinical response, reliably eradicate pathogens and limit the potential for development of resistance. SmithKline Beecham welcomes future opportunities to work with FDA to address these important issues.

If there are any questions regarding these comments, please contact me at (215) 751-7755.

Respectfully submitted,

Robert G. Pietrusko, Pharm.D., Vice-President
Anti-Infective & Anti-Viral Therapeutic Areas
U.S. Regulatory Affairs

REFERENCES

1.) Dowell, S.F., Butler, J.C., Giebink, G.S., et. al.: "Acute Otitis Media: Management and Surveillance in an Era of Pneumococcal Resistance - a Report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group", Pediatr Infect Dis, 18: 1-9, 1999.
2.) Sinus and Allergy Health Partnership: "Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis", Otolaryngol-Head and Neck Surgery 123 (suppl 1, part 2):S1-32, 2000.
3.) Cabana, M.D, Rand, C.S., Powe, N.R., et. al.: "Why Don't Physicians Follow Clinical Practice Guidelines? - A Framework for Improvement", JAMA, 282 (no. 15): 1458-65, 1999.
4.) FDA Reminds Prescribers of Important Considerations Before Prescribing Flu Drugs, FDA TALK PAPER, January 12, 2000.
5.) CDC, FDA, NIH: "Draft Public Health Action Plan to Combat Antimicrobial Resistance", Federal Register, 65 (no. 121), 38832-3, June 22, 2000.
6.) FDA Anti-Infectives Advisory Committee Meeting: "Development of Drugs for Resistant Bacteria Including Selective Spectrum Agents", October 15 - 16, 1998.

200 North 16th Street, Philadelphia, PA. 19102

Sender
Robert G. Pietrusko, Pharm.D. Mail code FP1005

Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

1D-487

Phone:

COURIER/RECEIVING
SMITHKLINE BEECHAM
200 NORTH 16th STREET
PHILADELPHIA PA 19102
(215)751-5855

SHIP DATE: 01DEC00
ACC # 168787991

ACTUAL WGT: 1 LBS SCALE

SEE ADDRESS LABEL ON PACKAGE FOR
THIS SHIPMENT TO MD 20852

4661 5007 2229 FedEx RELEASE # 0135823

REF: PH1005/WASHINGTON NC

PRIORITY OVERNIGHT MON

cad # 0011682 01DEC00

Deliver by:
04DEC00

TRK# 4661 5007 2229 FORM 0201

IAD AA

20852 -MD-US 19 GAIA

153076 NRIT 10/00

The World On Ti